Year: 2010

Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial

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Abstract: OBJECTIVES: We aimed to assess the predictive value of the SYNTAX score (SXscore) for major adverse cardiac events in the all-comers population of the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. BACKGROUND: The SXscore has been shown to be an effective predictor of clinical outcomes in patients with multivessel disease undergoing percutaneous coronary intervention. METHODS: The SXscore was prospectively collected in 1,397 of the 1,707 patients enrolled in the LEADERS trial (patients after surgical revascularization were excluded). Post hoc analysis was performed by stratifying clinical outcomes at 1-year follow-up, according to 1 of 3 SXscore tertiles. RESULTS: The 1,397 patients were divided into tertiles based on the SXscore in the following fashion: SXscore<or=8 (SXlow) (n=464), SXscore>8 and <or=16 (SXmid) (n=472), and SXscore>16 (SXhigh) (n=461). At 1-year follow-up, there was a significantly lower number of patients with major cardiac event-free survival in the highest tertile of SXscore (SXlow=92.2%, SXmid=91.1%, and SXhigh=84.6%; p<0.001). Death occurred in 1.5% of SXlow patients, 2.1% of SXmid patients, and 5.6% of SXhigh patients (hazard ratio [HR]: 1.97, 95% confidence interval [CI]: 1.29 to 3.01; p=0.002). The myocardial infarction rate tended to be higher in the SXhigh group. Target vessel revascularization was 11.3% in the SXhigh group compared with 6.3% and 7.8% in the SXlow and SXmid groups, respectively (HR: 1.38, 95% CI: 1.1 to 1.75; p=0.006). Composite of cardiac death, myocardial infarction, and clinically indicated target vessel revascularization was 7.8%, 8.9%, and 15.4% in the SXlow, SXmid, and SXhigh groups, respectively (HR: 1.47, 95% CI: 1.19 to 1.81; p<0.001). CONCLUSIONS: The SXscore, when applied to an all-comers patient population treated with drug-eluting stents, may allow prospective risk stratification of patients undergoing percutaneous coronary intervention. (LEADERS Trial Limus Eluted From A Durable Versus ERodable Stent Coating; NCT00389220).

DOI: https://doi.org/10.1016/j.jacc.2010.03.044

P; Windecker, S; Serruys, P W (2010). Value of the SYNTAX score for risk assessment in the all-comers population of the randomized multicenter LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial. Journal of the American College of Cardiology, 56(4):272-277.
DOI: https://doi.org/10.1016/j.jacc.2010.03.044

Value of the SYNTAX score (SX) for risk assessment in the "all-comers" population of the randomized multicenter LEADERS trial.

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Word count: 2,508

Funding: Biosensors Europe SA, Switzerland

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Keywords: SYNTAX score, prognostic value, biolimus-eluting stent, sirolimus-eluting stent, biodegradable polymer, target vessel revascularization, major adverse cardiac event

Abbreviations :

SXscore : SYNTAX score

SXlow : SYNTAX score ≤8

SXmid : SYNTAX score >8 and ≤16

SXhigh : SYNTAX score >16

SES : sirolimus eluting stent

BES : biolimus eluting stent

TLR : target lesion revascularization

TVR : target vessel revascularization

MACE : major adverse cardiac events

MI : myocardial infarction

HR : hazard ratio

RVD : reference vessel diameter

MLD : minimal lumen diameter

Abstract:

Background: The SYNTAX score (SXscore) has been shown to be an effective predictor of clinical outcomes in patients with multivessel disease undergoing percutaneous coronary intervention (PCI).

Objective: We aimed at assessing the predictive value of the SXscore for major adverse cardiac events in the "all-comers" population of the LEADERS trial.

Methods: The SXscore was prospectively collected in 1,397 of the 1,707 patients enrolled in the LEADERS trial (patients post-surgical revascularization were excluded). Post-hoc analysis was performed by stratifying clinical outcomes at 1 year follow-up, according to one of three SYNTAX score tertiles.

Results: 1,397 patients were divided into tertiles based on the SYNTAX score in the following fashion: SXlow ≤8 (n=464), 8 <SXmid ≤16 (n=472) and SXhigh >16 (n=461).

At 1 year follow-up there was a significantly lower number of patients with MACE-free survival in the highest tertile of SX score (SXlow=92.2%, SXmid=91.1% and SXhigh=84.6%; p<0.001). Death occurred in 1.5% of patients with SYNTAX scores of <8, 2.1% of patients with intermediate scores of > 8 to 16 and 5.6% of patients with high scores of >16 (HR 1.97 CI 1.29-3.01; p=0.002). Myocardial infarction rate tended to be higher in the SXhigh group. TVR was 11.3% in the SXhigh group versus 6.3% and 7.8% in the SXlow and SXmid groups, respectively (HR 1.38; CI 1.1-1.75; p=0.006). Composite of cardiac death, myocardial infarction and clinically indicated TVR was 7.8%, 8.9% and 15.4% in the SXlow, SXmid and SXhigh, respectively (HR 1.47; CI 1.19-1.81; p<0.001).

Kommentar [TDV1]: Because of 7.8% MACE

Conclusions: The SYNTAX score, when applied to an all-comers patient population treated with drug eluting stents, may allow for prospective risk stratification of patients undergoing PCI.

Introduction:

The SYNTAX score (SXscore) is a comprehensive angiographic scoring system that is derived entirely from the coronary anatomy and lesion characteristics.(1-3) It was initially designed to quantify lesion complexity, however, it is also able to predict major adverse cardiac events (MACE) following percutaneous revascularization in patients with multivessel coronary artery disease(4-6) and/or left main disease.(7) More recent data indicates its ability to predict peri-procedural myocardial infarction (MI) in patients undergoing elective percutaneous coronary intervention (PCI). (8) In this sub-study of the LEADERS trial (Limus Eluted from A Durable versus ERodable Stent coating), where the SXscore was collected prospectively in 1,397 "all-comer" patients, we assessed its prognostic value for MACE events at 1 year follow-up.

Kommentar [C2]: Possibly include Capadanno ref here as well?

Methods:

Study population: LEADERS was a multicenter European non-inferiority trial comparing the safety and efficacy of the BioMatrix™ Flex biolimus eluting stent with a biodegradable polymer (BES) (Biosensors, Morges, Switzerland) to the Cypher® Select™ sirolimus eluting stent with a durable polymer (SES) (Cordis, NJ, USA) in 1,707 'all-comers' patients. Detailed study protocol can be found in the main manuscript.(9) The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent for participation in the trial.

SXscore and angiographic analysis: From the baseline diagnostic angiogram, each coronary lesion producing ≥50% diameter stenosis in vessels ≥1.5 mm was scored separately and added together to provide the overall SXscore, which was calculated prospectively using the SXscore algorithm (described in full elsewhere).(1-3) All angiographic variables pertinent to SXscore calculation were computed by blinded core laboratory analysts (Cardialysis B.V., Rotterdam, The Netherlands). The SXscore is not currently validated in patients with acute myocardial infarction or previous PCI and CABG. Core lab analysts were blinded to all clinical data and therefore patients with occluded infarct related arteries were scored as occlusions of unknown duration in a similar manner to any chronically occluded artery. Those patients with in-stent restenosis lesions were scored in the same manner as if the lesion was a *de novo* lesion.

Study endpoints: Definitions of all endpoints are provided elsewhere.(9) The primary endpoint of this sub-study was MACE, defined as the composite of cardiac death, MI, and clinically-indicated target vessel revascularization (TVR) within 9-months. Secondary endpoints were any target lesion revascularization (TLR) (both clinically and non-clinically indicated), any TVR,

Kommentar [TDV3]: The manuscript is for 12M, but primary endpoint was 9M fup

cardiac death, death from any cause, myocardial infarction, stent thrombosis (defined according to the Academic Research Council(10)), device success, and lesion success.

The pre-specified principal outcome of the angiographic sub-study was in-stent percent diameter stenosis. Secondary angiographic outcomes were in-segment percent diameter stenosis, minimal lumen diameter, late lumen loss, and binary restenosis.

Statistical analysis: A stratified post-hoc analysis of clinical and angiographic outcomes was performed according to the tertiles of the SYNTAX score.(4,5) Dedicated software and visual coronary angiography served to determine the SYNTAX score.(1,2) All randomized patients without prior surgical revascularisation (1397/1707), were included in the analysis. Angiographic outcomes were analyzed using SAS v8 Proc Mixed for continuous and Proc Genmod for binominal outcomes, taking into account the within-patient correlation structure of these data. The Cox proportional hazards model was used to compare clinical outcomes between the groups. All analyses were performed using SAS 8.02 by a dedicated statistician. All p-values and CIs were two-sided. Multivariate model included SXscore, diabetes, beta-blocker use, stent type and presence of acute coronary syndrome as covariates. Testing for (linear) trend was done by using Generalized Linear Models with SX-class as a covariable for continuous variables and the Cochran-Armitage test for trend in categorical data.

Results:

SXscore and baseline characteristics: The SXscore was collected prospectively in 1,397 of the 1,707 patients (81.8%) enrolled in the LEADERS trial. The score ranged from 0 to 49, with a mean $\pm$ SD of 13.5$\pm$8.7, and a median of 12 (inter-quartile range of 12; 7 to 19). In this post-hoc analysis, the SXscore tertiles were defined as: SXlow $\leq$8 (n=464), 8< SXmid $\leq$16 (n=472) and SXhigh >16 (n=461). Baseline clinical and angiographic characteristics of the patients are listed in table 1 and 2.

One year outcomes: SXscore significantly predicted the rate of MACE at 360 days (Table 3; Figures 1-4). There was a lower number of patients with MACE-free survival in the highest tertile of SYNTAX score (SXlow=92.2%, SXmid=91.1% and SXhigh=84.6%; p<0.001). Death occurred in 1.5% of patients with SXlow, 2.1% of patients with SXmid and 5.6% of patients with SXhigh (HR 1.97 CI 1.29-3.01; p=0.002). The rate of MI tended to be higher in patients with SXhigh (HR MI 1.2 CI 0.9-1.61; p=0.22). TVR was 11.3% in the SXhigh group versus 6.3% and 7.8% in the SXlow and SXmid groups, respectively (HR 1.38; CI 1.1-1.75; p=0.006). Composite of cardiac death, myocardial infarction and clinically indicated TVR was 7.8%, 8.9% and 15.4% in the SXlow, SXmid and SXhigh, respectively (HR 1.47; CI 1.19-1.81; p<0.001).

Multivariate model: In a multivariate model, SXscore remained a significant predictor of MACE and mortality. Patients in the SXhigh group had a 50% higher chance of the composite of cardiac death, MI and clinically indicated TVR than patients in the SXmid group (p<0.001); which was comparable to the 51% higher composite event rate among diabetics (p=0.022). Use of BES tended to reduce the composite event rate by 26% (p=0.07).

Stent thrombosis rates: The rate of definite stent thrombosis was 0.9%, 2.1% and 3.5% in the SXlow, SXmid and SXhigh, respectively

Discussion:

Complexity of disease and lesion characteristics are well recognized predictors of peri-procedural complications(8) and long-term mortality.(11-13) The SXscore was developed to comprehensively assess lesion characteristics and is based on the combination of classifications from the AHA/ACC, modified BARI classification, chronic total occlusion and bifurcation scores and Leaman classification.(1) It has previously been applied in both the SYNTAX trial and the ARTS-II study, which both demonstrated the good predictive value of the SXscore in patients with multivessel disease, with the highest tertile patients having significantly more MACE events during short(4,5) and long-term follow-up.(6)

Kommentar [C4]: Need to mention capadonno CUSTOMISE registry here.

This study is the first to report the utility of the SXscore as a predictor of MACE, including cardiac death, in an "all-comers" population including patients with acute coronary syndromes. Overall this patient population had a much lower SYNTAX scores than the SYNTAX trial population, however, despite this the SYNTAX score still appears to have good discriminatory power for risk assessment.

Kommentar [C5]: AUTAX probably needs a mention, but mainly to dismiss it, and its results as it was small study which split patients into 4 groups. Not really a SYNTAX score assessment. Wijn's editorial has some good points.

Limitations:

The limitation of the SXscore is that it does not incorporate clinical patient characteristics. Patients with prior CABG have not been included as the SX score algorithm is only currently available for patients with *de novo* disease. Modifications to the SXscore for risk stratification in patients post-CABG are currently being developed. The SXscore of patients who presented with acute MI, or had had previous PCI were included in this analysis, despite no previous validation

in these patients. This study may suffer from limitations inherent to subgroup analysis (chance findings and under-powering).(14,15) (16)

Conclusion:

This study demonstrates that the prognostic value of the SYNTAX score is valid for all patients with *de novo* coronary artery disease undergoing percutaneous revascularisation.

Table 1. Baseline clinical characteristics

Baseline clinical variables, n(%)	SX score <8 N=464	SX score 8-16 N=472	SX score >16 N=461	p-value on Trend (2-sided)
Age >65 (%)	210 (45.3%)	224 (47.5 %)	239 (51.8%)	0.048
Male	346 (74,6%)	344 (72.9%)	340 (73.8%)	0.79
Diabetes	93 (20.0%)	117 (24.8%)	111 (24.1%)	0.15
Current smoking	134 (28.9%)	121 (25.6%)	126 (27.3%)	0.61
Hypertension	353 (76.1%)	353 (74.8%)	324 (70.3%)	0.048
Hypercholesterolemia	314 (67.7%)	314 (66.5%)	285 (61.8%)	0.06
Family history	201 (43.3%)	188 (39.8%)	168 (36.4%)	0.034
Renal insufficiency	17 (3.7%)	21 (4.5%)	28 (6.1%)	0.09
Previous MI	132 (28.5%)	145 (30.7%)	137 (29.7%)	0.69
Previous PCI	179 (38.6%)	165 (35.0%)	147 (31.9%)	0.036
PVD	26 (5.6%)	36 (7.6%)	31 (6.7%)	0.51
Previous Stroke	13 (2.8%)	19 (4.0%)	16 (3.5%)	0.59
Clinical presentation:				
Stable	146 (31.5%)	154 (32.6%)	108 (23.4%)	0.008
Unstable	127 (27.4%)	89 (18.9%)	88 (19.1%)	0.002
STEMI	46 (9.9%)	90 (19.1%)	**128 (27.8%)**	**<0.0001**
Non-STEMI	90 (19.4%)	90 (19.1%)	97 (21.0%)	0.54
Silent Ischaemia	55 (11.9%)	49 (10.4%)	40 (8.7%)	0.12

Kommentar [TDV6]: I made it 2 digits behind comma/ 3 digits If <0.06

Kommentar [TDV7]: Data were for FEMALE, MALE was the complement, so 74.6 and not 25.4

Table 2. Baseline angiographic characteristics:

Angiographic variable	SX score <8	SX score 8-16	SX score >16	p-value
No. of diseased lesions per patient (based on SYNTAX application)	1.47±0.66	2.37±1.00	3.45±1.44	<0.001
No. of treated lesions per patient (as defined by Corelab)	1.2±0.46	1.47±0.7	1.69±0.86	<0.001
Ratio of diseased to treated lesions	1.22	1.61	2.04	n/a
Coronary artery treated				
LAD	162 (34.9%)	242 (51.3%)	296 (64.2%)	<0.001
LCX	140 (30.2%)	144 (30.5%)	164 (35.6%)	0.079
RCA	216 (46.6%)	209 (44.3%)	174 (37.7%)	0.007
2-vessel disease	49 (10.6%)	102 (21.6%)	138 (29.9%)	<0.001
3-vessel disease	3 (0.7%)	13 (2.8%)	23 (5.0%)	<0.001
Stent type				
Biolimus	229 (49.3%)	235 (49.8%)	239 (51.8%)	0.45
Sirolimus	235 (50.7%)	237 (50.2%)	222 (48.2%)	0.45
Number of implanted stents	1.47±0.8	1.90±1.12	2.33±1.39	<0.001
Total stent length/patient (mm)	25.9±16.5	34.2±21.7	42.9±26.2	<0.001
Chronic total occlusion	6 (1.3%)	10 (2.1%)	19 (4.1%)	0.006
Moderate to severe calcification	23 (5.1%)	96 (20.3%)	184 (39.9%)	<0.001
Bifurcation lesion	57 (12.3%)	161 (34.1%)	184 (39.9%)	<0.001
Use of 2b3a	80 (17.2%)	113 (23.9%)	154 (33.4%)	<0.001

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